II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

In response to the Restriction Requirement dated October 2, 2002, Applicants elected the Group I claims (which included claims 1-6, 14-18, 28-38, and 52) and traversed the restriction with respect to Groups I, II, and III. The examiner reconsidered the restriction, which Applicants appreciate, and rejoined Groups I, II, and III, regarding ICAM-1, VCAM and E-selectin as species.

Claims 1-6, 14-18, and 28-37 were considered to read on all of the species. The Action indicates that claims 38 and 52 were not properly part of Group I, contending that claim 38 belongs in Group XIV and Group 52 belongs in Groups XV-XVII. Therefore, claims 1-6, 14-18, and 28-37 were examined with respect to the Office Action dated April 9, 2003. Claims 7-13, 19-27, and 38-62 were canceled without prejudice or disclaimer in the Amendment disclosed herein as these claims are drawn to nonelected inventions.

Claims 1 and 16 have been amended without prejudice or disclaimer. New claims 63-68 have been added. Support for the amendments and new claims may be found throughout the Specification, and more particularly, in the figures. Therefore, claims 1-6, 14-18, 28-37, and 63-68 are pending.

B. The Claim Rejections Under 35 U.S.C. §112, Second Paragraph, are Overcome

The Action rejects claims 1-6, 14-18, and 28-37 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that the applicants regard as the invention. The Action contends that claim 1 is

incomplete because it omits a step related to determining modulation. The Action also states that no proper controls are set up to compare the inhibition/enhancement of adhesion molecules. Applicants traverse.

Applicants draw the Examiner's attention to present claim 1, which includes the step "assaying for an interaction between the C-reactive protein and the first candidate substance with an assay that determines modulation of C-reactive protein-induced expression of a molecule relative to C-reactive protein-induced expression of the molecule in the absence of the first candidate substance; and determining whether any modulation of C-reactive protein induced expression of the molecule occurs."

In addition, the language of claim 1 cited above includes information as to proper controls to assess the modulation of C-reactive protein function, since C-reactive protein-induced expression of a molecule is determined relative to C-reactive protein-induced expression of the molecule in the absence of the candidate substance. Support this limitation in claim 1 can be found throughout the Specification, such as on page 4, lines 12-27.

In view of the above, the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

C. The Claim Rejections Under 35 U.S.C. §112, Second Paragraph, are Overcome

1. The Rejections for Lack of Written Description are Overcome

The Action rejects claims 1-6, 14-18, and 28-37 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. More particularly, it contends that Applicants were not in possession of any

method of screening for modulators of any C-reactive protein because the application discloses only a human C-reactive protein and the skilled artisan cannot envision all the contemplated C-reactive protein possibilities covered by the claims. Applicants traverse this rejection.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. *Manual of Patent Examining Procedure*, §2163, citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

The Action appears to admit that there is adequate written description support in the Specification for human C-reactive protein. Office Action, page 5, section 8, paragraphs 2 and 4.

Applicants draw the Examiner's attention to independent claim 1, which pertains to a method of screening for modulators of human C-reactive protein, which includes the step of obtaining a C-reactive protein. Each of the remaining claims at issue in this rejection each depend from claim 1, and thus include the limitation that the claimed methods pertaining to human C-reactive protein. Thus, because each of the claims pertains to human C-reactive protein, there is adequate written description support.

Evidence for this written description support can be found throughout the entire Specification. Specifically, there is adequate written description support in the Specification not only for human C-reactive protein, but also for *in vivo* methods and for methods that do not involve the use of serum. For example, Example 1 (Specification, page 33, line 21 through page 34, line 2) provides information pertaining to HUVEC cell culture and general information pertaining to C-reactive protein, which can be applied by one of ordinary skill to the claimed methods. Example 2 provides details pertaining to how to conduct the claimed screening

methods, and provides guidance which can be applied in both *in vitro* as well as i*n vivo* screening methods. Specification, page 34, lines 5-17. Example 3 provides information pertaining to measurement of the induction of an adhesion molecule, a receptor, a signaling molecule, a cytokine, or an enzyme in the presence of serum. Specification, page 34, line 18 through page 36, line 2. In addition, information pertaining to the detection of adhesion molecules in the absence of serum in provided in Example 4. Specification, page 36, line 3 through page 37, line 3. Example 5 provides information pertaining to the detection of chemokines in the presence of serum. Specification, page 37, lines 4-25. Example 6 provides information pertaining to the modulation of C-reactive protein effects by statin and PPAR activators. Specification, page 38, lines 1-24.

Because the Specification describes in claimed invention in sufficient detail that one skilled in the art could conclude that the inventors had possession of the claimed invention, the written description requirement has been satisfied. Therefore, in view of the above, Applicants request that the written description rejections under 35 U.S.C. 112, first paragraph, should be withdrawn.

2. The Rejections for Lack of Enablement are Overcome

The Action rejects claims 1-6, 14-18, and 28-37 under 35 U.S.C. § 112, first paragraph, as not reasonably providing enablement for a method of screening for modulators of any C-reactive protein. More specifically, the Action alleges that the Specification does not show that the methods are capable of function as is disclosed because of an issue involving serum factors, and contends that the Specification fails to provide any guidance as to how to make and use every C-reactive protein and/or every adhesion molecule. The Action argues that protein

chemistry is one of the most unpredictable areas of biotechnology, and consequently, there is insufficient disclosure of all C-reactive protein molecules that maintain the structural and functional properties of the human C-reactive protein. It concludes that it would require undue trial and error to practice the claimed invention in view of the quantity of experimentation necessary, the working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breath of the claims. Applicants traverse this rejection.

The test of enablement is whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (CCPA 1976); *MPEP* §2164.01. For the reasons set forth below, the instant Specification meets these requirements.

a. The Specification Provides Substantial Information to Enable the Claimed Invention

The Specification contains substantial information regarding the subject matter of the claims that is more than sufficient to allow one of ordinary skill in the art to make and use the claimed invention without undue experimentation.

Support for the claimed invention can be found throughout the Specification. As noted above, Example 1 (Specification, page 33, line 21 through page 34, line 2) provides information pertaining to HUVEC cell culture and general information pertaining to C-reactive protein, which can be applied by one of ordinary skill to the claimed methods. Example 2 provides details pertaining to how to conduct the claimed screening methods. Specification, page 34, lines 5-17. Example 3 provides information pertaining to measurement of the induction of an adhesion molecule, a receptor, a signaling molecule, a cytokine, or an enzyme in the presence of

serum. Specification, page 34, line 18 through page 36, line 2. In addition, information pertaining to the detection of adhesion molecules in the absence of serum in provided in Example 4. Specification, page 36, line 3 through page 37, line 3. Example 5 provides information pertaining to the detection of chemokines in the presence of serum. Specification, page 37, lines 4-25. Example 6 provides information pertaining to the modulation of C-reactive protein effects by statin and PPAR activators. Specification, page 38, lines 1-24.

b. There is Enablement for Human C-Reactive Protein, In Vivo Methods, and Methods that Do Not Involve Use of Serum

The methods of screening for modulators of the claimed invention pertain specifically to methods of screening for modulators of ***human C-reactive protein***. The steps of the claimed methods include obtaining a human C-reactive protein, contacting the C-reactive protein with at least a first candidate substance, assaying for an interaction between the C-reactive protein and the first candidate substance with an assay that determines modulation of C-reactive protein-induced expression of a molecule relative to C-reactive protein-induced expression of the molecule in the absence of the first candidate substance, and determining whether any modulation of C-reactive protein induced expression of the molecule occurs.

The Examples in the Specification cited above provide substantial information pertaining to human C-reactive protein, the effect of serum on the methods, and *in vitro* methods. Consequently, the Specification contains information regarding the subject matter of the claims that is more than sufficient to allow one of ordinary skill in the art to make and use the claimed invention without undue experimentation.

It is not necessary for the Specification to provide a specific example of ***every*** C-reactive protein and ***every*** method that does not involve use of serum for the enablement requirement to

be satisfied. Nor is it necessary for the Specification to provide examples of ***in vivo*** methods of the claimed invention. As long as the Specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); *Manual of Patent Examining Procedure* §2164.01(b). Because the Specification, and the sections cited above, provides ample evidence of the claimed methodologies that bears a reasonable correlation to the entire scope of the claims, the enablement requirement is satisfied.

c. No Undue Experimentation is Required to Practice the Claimed Invention

As discussed above, the Specification, particularly the cited working Examples, provides sufficient guidance to those of ordinary skill in the art to practice the claimed methods of screening for modulators of human C-reactive protein, and not merely *in vitro* methods in serum. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). No undue experimentation would be required for one of ordinary skill in the art to practice the claimed invention, in view of the disclosure in the Specification.

In view of the above, the Specification provides sufficient enablement for the claimed invention. Accordingly, Applicants request that the enablement rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

3. The Present Claims are Allowable

The Action appears to suggest that there is adequate written description and enablement of claims pertaining to an *in vitro* method of screening for modulators of human C-reactive protein. Applicants draw the Examiner's attention to new independent claim 63, and new dependent claims 64-68, which include each of these limitations. By adding these new claims, Applicants in no way admit that the other claims of this application are not allowable.

Although each of the present claims, as written, pertains to human C-reactive protein, Applicants in no way aquiesce to any assertion that other claims directed to non-human C-reactive proteins would not be allowable. In fact, Applicants strongly disagree that such claims would not be allowable. The entire Specification, including each of the sections of the Specification cited above, provides adequate written description and enablement support not only for human C-reactive protein, but for other C-reactive proteins as well as *in vivo* methods and methods that do not involve the use of serum. Applicants reserve the right to seek allowance of such claims and to set forth arguments in support of such claims at a later date should they so desire.

D. The Rejections Under 35 U.S.C. 102(b) are Overcome

1. Claims 1, 14, and 32 Are Novel over Tseng *et al.*

The Action rejects claims 1, 14, and 32 under 35 U.S.C. § 102(b) as being anticipated by Tseng *et al.* ("Tseng"), which is said to teach of method of screening for modulators of C-reactive protein using C-reactive protein from human ascites fluid and contacting the C-reactive protein with different monoclonal antibodies and assaying for an interaction. Applicants traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). See also *MPEP*, §2131. "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q. 1913, 1920 (Fed. Cir. 1989).

Tseng fails to anticipate the claimed invention because Tseng *et al.* fails to teach, either expressly or inherently, the limitation "assaying for an interaction between the C-reactive protein and the first candidate substance with an assay that determines modulation of C-reactive protein-induced expression of a molecule relative to C-reactive protein-induced expression of the molecule in the absence of the first candidate substance, and determining whether any modulation of C-reactive protein induced expression of the molecule occurs."

Tseng fails to demonstrate any inhibition or enhancement of C-reactive protein-induced expression of any molecule as a result of contacting the C-reactive protein with the disclosed monoclonal antibodies. It merely discloses modulation of binding of C-reactive protein to fibronectin. It does not disclose any inhibition or enhancement of C-reactive protein-induced expression of fibronectin or any other molecule as a result of contacting the monoclonal antibody with C-reactive protein.

Therefore, because Tseng fails to each limitation of the claimed invention, this rejection should be withdrawn.

2. Claims 1, 14, 28 and 32 Are Novel over Cermak *et al.*

The Action rejects claims 1, 14, 28, and 32 under 35 U.S.C. § 102(b) as being anticipated by Cermak *et al.* ("Cermak"). This reference is alleged to teach a method of screening for

modulators of C-reactive protein by contacting human C-reactive protein with tissue factor and assaying for production of C-reactive protein. Applicants traverse this rejection.

As noted above, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). See also *MPEP*, §2131. "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q. 1913, 1920 (Fed. Cir. 1989).

Cermak fails to anticipate the claimed invention because it fails to disclose, either expressly or inherently, each and every element of the claimed invention. In particular, as with Tseng discussed above, Cermak fails to teach the limitation "assaying for an interaction between the C-reactive protein and the first candidate substance with an assay that determines modulation of C-reactive protein-induced expression of a molecule relative to C-reactive protein-induced expression of the molecule in the absence of the first candidate substance; and determining whether any modulation of C-reactive protein induced expression of the molecule occurs."

Cermak fails to demonstrate modulation of C-reactive protein-induced expression of a molecule as a result of the contact between the human C-reactive protein and the tissue factor disclosed in Cermak.

Furthermore, the Action notes that Cermak teaches that actinomycin D, cycloheximide, and anti-human C-reactive protein inhibited C-reactive protein-induced procoagulant activity (PCA). However, no specific modulation of a C-reactive protein-induced expression of a molecule was expressly or inherently disclosed in Cermak. Further, Cermak notes that a variety of factors, such as cytokines, LPS, or activated complement, may influence tissue factor

synthesis, hence PCA. See Cermak, page 518, paragraph 1. Cermak failed to address each of these factors as possible mediators of the observed alterations in PCA.

Therefore, since Cermak fails to expressly or inherently disclose each and every limitation of the claimed invention, Cermak fails to anticipate. Therefore, this rejection is overcome.

E. The Rejections Under 35 U.S.C. §103(a) are Overcome

The Action rejects claims 1, 14-18, 28, and 32 under 35 U.S.C. §103 as being obvious over Tseng or Cermak, in view of U.S. Patent 6,455,046 ("the '046 patent"). Tseng and Cermak have been discussed previously. The '046 patent is said to teach that native C-reactive protein can be obtained from natural sources and recombinant DNA techniques. The '046 patent is also said to teach that the C-reactive protein can be obtained from these sources with about 99% purity. According to the Action, it would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the C-reactive protein taught by Tseng or Cermak from a cell, a recombinant DNA technique, or human serum as taught by the '046 patent. The Action therefore indicates that, from the combined teachings of the references, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure § 2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if one element is missing, a *prima facie* case of obviousness does not exist.

There is no *prima facie* case of obviousness because the prior art references fail to teach or suggest all of the claim limitations. As discussed above, neither Tseng nor Cermak teaches the element "assaying for an interaction between the C-reactive protein and the first candidate substance with an assay that determines modulation of C-reactive protein-induced expression of a molecule relative to C-reactive protein-induced expression of the molecule in the absence of the first candidate substance; and determining whether any modulation of C-reactive protein induced expression of the molecule occurs."

Furthermore, the '046 patent fails to provide the missing information by teaching this claim limitation. The '046 patent pertains to methods of enhancing an immune response to an immunogen in an animal. It does not teach the limitation of contacting a candidate substance with a first candidate substance, nor does it teach modulation of C-reactive protein-induced expression of any molecule.

Furthermore, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The '046 patent only pertains to methods of enhancing an immune response. As noted above, it provides no teaching pertaining to contacting a candidate substance with C-reactive protein that results in modulation of C-reactive protein-induced

expression of any molecule. Furthermore, there is no motivation in the references themselves or in the knowledge available to one of ordinary skill in the art, to modify the teachings to result in the claimed invention.

For all of these reasons, there is no *prima facie* case of obviousness. Consequently, this rejection should be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner and the undersigned attorney at 512-536-3081 is requested.

III. REQUEST FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of two months to an including September 9, 2003, in which to respond to the Office Action dated April 9, 2003.

Pursuant to 37 C.F.R. § 1.17, a check for the process fee for a two-month extension of time is enclosed.

If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/UTSH:249US.

Respectfully submitted,

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